PTO/SB/33 (07-05)
Approved for use through xx/xx/200x. OMB 0651-00xx
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number: 13751-0055US1
	Application Number 10/540,959	Filed April 4, 2006
	First Named Inventor Paul D. Rennert	
	Art Unit 1644	Examiner Maher M. Haddad

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record 47,443
(Reg. No.)

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34

/Jack Brennan/
Signature

Jack Brennan
Typed or printed name

(212) 765-5070
Telephone number

April 20, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ Total of no. forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Paul D. Rennert	Art Unit	: 1644
Serial No.	: 10/540,959	Examiner	: Maher M. Haddad
Filed	: April 4, 2006	Conf. No.	: 5124
Title	: KIM-1 ANTAGONISTS AND USE TO MODULATE IMMUNE SYSTEM		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicant submits this request under the Pre-Appeal Conference Pilot Program described in the U.S. Patent and Trademark OG Notice, "New Pre-Appeal Brief Conference Pilot Program," dated July 12, 2005, and extended until further notice as of January 10, 2006. This request is being filed with a Notice of Appeal.

Status of Claims and Summary of Rejections

Claims 44, 45, 47, and 55-59 are pending in the application. Claims 44 and 57 have been withdrawn from consideration. In the final Office Action dated November 19, 2008, claims 45, 47, 55, 56, 58, and 59 were rejected as not enabled. Applicant filed a response to the Office Action on February 19, 2009. In an Advisory Action dated March 12, 2009, the rejection of the claims was maintained.

35 U.S.C. §112, First Paragraph (Enablement)

At pages 2-3 of the final Office Action, claims 45, 47, 55, 56, 58, and 59 were rejected as allegedly not enabled. According to the final Office Action,

> the specification, while being enabling for a method of treating inflammatory bowel disease with KIM-1-Ig fusion protein, does not reasonably provide enablement for a method of treating an autoimmune disease/immunological disorder in a subject comprising administering an antagonist antibody or antigen-binding fragment thereof that binds to KIM-1, wherein the immunological disorder/disease is inflammatory bowel disease…

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: April 20, 2009

Independent claim 45 is directed to a method of treating an immunological disorder in a subject, the method comprising administering to the subject an effective amount of a composition comprising an antagonist antibody or antigen-binding fragment thereof that binds to KIM-1, wherein the immunological disorder is arthritis or an inflammatory bowel disease. Claims 47, 55, 56, 58, and 59 depend directly or indirectly from claim 45. It is applicant's understanding that examination of the claims has been limited to treatment of an inflammatory bowel disease (i.e., the elected species of "immunological disorder").

The inventor of the present application has discovered that KIM-1 antagonists interfere with T cell activation, suppress IgG response to antigen, and are therapeutically effective in a mouse model of inflammatory bowel disease. In view of these experimental findings, the person of ordinary skill in the art at the time the present application was filed would have reasonably expected antagonist anti-KIM-1 antibodies to be effective in the treatment of inflammatory bowel diseases and the other immunological disorders recited in the claims. Applicant respectfully contests the final Office Action's assertion (at page 2) that "[t]he specification does not provide any evidence that KIM-1 antagonist antibodies would function to [treat] IBD such as ulcerative colitis, ileitis or Crohn's disease" (emphasis added).

The dextran sulfate sodium (DSS) model of inflammatory bowel disease described in Example 12 of the present application is an art-accepted *in vivo* animal model system for inflammatory bowel disease. An *in vivo* animal model example described in the specification constitutes a "working example" if that example correlates with the claimed invention. MPEP § 2164.02. "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." *Id.* Because of the art acceptance of the DSS mouse model for inflammatory bowel disease, the specification (i.e., Example 12) contains a working example indicating that a KIM-1-Ig fusion protein can be used effectively in the treatment of inflammatory bowel disease. Although the working example describes the use of a soluble KIM-1 protein, whereas the claimed methods are directed to the use of an anti-KIM-1 antagonist antibody, the person of ordinary skill in the art having read applicant's experimental findings would have understood that *any* means of blocking KIM-1 function would be an effective means of treating an inflammatory bowel disease. As is described in the application and as is common

in the field of immunology, KIM-1 blockade could be accomplished without undue experimentation either by administration of a soluble KIM-1 protein (as exemplified in Examples 11 and 12, respectively, in an *in vitro* mixed lymphocyte reaction and an *in vivo* animal model of inflammatory bowel disease) or by administration of an anti-KIM-1 antagonist antibody (as exemplified in Example 11 in an *in vitro* mixed lymphocyte reaction). The person of ordinary skill in the art would have reasonably expected that inhibition of the KIM-1 signaling pathway via administration of an anti-KIM-1 antagonist antibody to be (like administration of a soluble KIM-1 protein, described in Example 12) an effective means for treatment of an inflammatory bowel disease.

The majority of the final Office Action did not address the specification's disclosure of an *in vivo* working example of treatment of inflammatory bowel disease. Instead, most of the rejection relates to the Office Action's assertion (at page 3) that "the MLC assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses or treatment of IBD *in vivo*." Although the IFN-gamma secretion that occurs in a mixed lymphocyte reaction is the result of histoincompatibility between two cell types, a discovery that an antibody added to the *in vitro* cell culture reduces or suppresses the mixed lymphocyte reaction indicates that the antibody can be used to inhibit an immune response. Neither of the references cited final Office Action (in the final paragraph on page 3) suggests that an antibody that inhibits a mixed lymphocyte reaction *in vitro* would not be reasonably expected to inhibit an immune response *in vivo*. In addition, and as detailed in the preceding paragraph, the working examples contained in the specification as filed extend well beyond the disclosure of the results of a mixed lymphocyte reaction and demonstrate that a soluble KIM-1 protein is effective in an *in vivo* model of inflammatory bowel disease. The person of ordinary skill in the art having read the inventor's experimental results in treating a mouse model of inflammatory bowel disease would have reasonably expected that an antagonist anti-KIM-1 antibody would (like the KIM-1-Ig fusion protein) be effective in the treatment of inflammatory bowel disease as well as the other immunological disorders recited in the claims.

The Advisory Action cited publications of Xiao et al. (2007), Umetsu et al. (2005), Encinas et al. (2005), and Hoo et al. (2006) in support of the Examiner's assertion that "the antibodies either would not treat (Encinas et al.) or would exacerbate (Hoo et al.) the

autoimmune disease including IBD in a subject." As an initial matter, all of four these publications were published after the December 29, 2003, international filing date of the present application. As such, their citation by the Office in the present enablement rejection is contrary to the MPEP's instruction that "[i]n general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling." According to the MPEP, "[e]xceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application." Id. Nothing in the record suggests that these references are relevant to establishing what one skilled in the art would have known on or before the filing date of the present application.

Setting aside the question of whether the post-filing references relied on by the Examiner are relevant to the state of the art at the filing date of the application, they simply fail to suggest that a skilled person having read applicant's specification would have concluded that antagonist anti-KIM-1 antibodies could not be used effectively to treat an inflammatory bowel disease. Taken together, these post-filing publications merely establish what is common for many proteins expressed on the surface of immune system cells -- some antibodies against the protein can have inhibiting functions whereas other antibodies against the protein can have activating functions. In fact, Xiao et al. and Encinas et al. clearly confirm that some anti-KIM-1 antibodies inhibit immune responses. For example, Xiao et al. concludes that a particular anti-KIM-1 (also known as TIM-1) antibody "inhibited the generation of antigen-specific T cells, production of IFN-γ and IL-17, and development of autoimmunity" (see abstract of Xiao et al.). In addition, Encinas et al. demonstrates that an anti-TIM-1 antibody decreases inflammation in a mouse model of asthma (see abstract of Encinas et al.). The inhibitory activities of selected anti-KIM-1 antibodies described in Xiao et al. and Encinas et al. are directly contrary to the Examiner's assertions that anti-KIM-1 antibodies would either not treat or exacerbate an inflammatory bowel disease, and instead clearly confirm the present application's disclosure that antagonist anti-KIM-1 antibodies can be used to inhibit an immune response and can be used in the treatment of inflammatory bowel diseases and the other immunological disorders recited in the claims. It would have required only routine screening for the person of ordinary skill in the art at the time the present application was filed to select anti-KIM-1 antibodies that have antagonist

function (using, for example, the *in vitro* and *in vivo* systems described in the specification in Examples 11 and 12) and are useable in the claimed methods.

In view of the foregoing remarks, the person of ordinary skill in the art, at the time the present application was filed, would have been able to practice the claimed methods without undue experimentation and with a reasonable expectation of success.

CONCLUSIONS

Applicant submits that all claims are in condition for allowance, which action is requested. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-0055US1.

Respectfully submitted,

Date: April 20, 2009

/Jack Brennan/
Jack Brennan
Reg. No. 47,443

Fish & Richardson P.C.
Citigroup Center
52nd Floor
153 East 53rd Street
New York, New York 10022-4611
Telephone: (212) 765-5070
Facsimile: (212) 258-2291